REMARKS

In view of the following remarks, the Examiner is respectfully requested to withdraw the rejections and allow Claims 1, 3-4, 11-28, 41, and 62-84, the only claims pending and under examination.

Claims 1, 3-4, 11-28, 41, and 62-84 have been examined and rejected.

Claims 2, 5-10, 42-50, 53-56, and 58-61 have been canceled.

Claims 29-40, 51-52, and 57 have been withdrawn.

Accordingly, no new matter has been added. As no new matter has been added by way of these amendments, entry thereof by the Examiner is respectfully requested.

Withdrawn Rejections

The Applicants thank the Examiner for the withdrawal of the nonstatutory obviousness-type double-patenting rejection of Claims 1, 11, 12, 26, and 27 over claims 1-3 and 30 of U.S. Patent No. 7,149,574.

The Applicants thank the Examiner for the withdrawal of the nonstatutory obviousness-type double-patenting rejection of Claims 1, 23, 24, 70 and 71 over claims 1-3, 6, 7, 9, 10, 43, 44 and 59 of U.S. Patent No. 7,363,076.

The Applicants thank the Examiner for the withdrawal of the provisional nonstatutory obviousness-type double-patenting rejection of Claims 1, 23, and 24 over claims 1-4, 7-10, 14 and 15 of co-pending U.S. Application No. 10/917,270.

The Applicants thank the Examiner for the withdrawal of the provisional nonstatutory obviousness-type double-patenting rejection of Claims 1, 3, 4, 11-24, 27, 63-66 over claims 1, 2, 4, 6-8, 13-16, 30-50, 55-58, 63, 71-76, and 81 of co-pending U.S. Application No. 10/846,486.

The Applicants thank the Examiner for the withdrawal of rejection of Claims 1, 26 and 27 under 35 U.S.C. § 102(b) as being anticipated by Puskas (U.S. Patent No. 6,429,217).

Double Patenting

Claims 1, 26, and 27 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 6, 12, 15 and 19 of co-pending U.S. Application No. 11/060,643.

Solely in order to expedite prosecution, and in no way agreeing with the Examiner's assertions, a Terminal Disclaimer under 37 CFR 1.321 is herewith submitted to overcome this rejection.

Accordingly, the Applicants respectfully request that the provisional nonstatutory obviousness-type double-patenting rejection of Claims 1, 26, and 27 be withdrawn.

Claims 1, 3, 70, 78, 79, 81-84 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 9, 22 and 24 of co-pending U.S. Application No. 10/962,190 in view of Davies et al. (The J of Intl Med Research, 1988, 16, 173-181)

Solely in order to expedite prosecution, and in no way agreeing with the Examiner's assertions, a Terminal Disclaimer under 37 CFR 1.321 is herewith submitted to overcome this rejection.

Accordingly, the Applicants respectfully request that the provisional nonstatutory obviousness-type double-patenting rejection of Claims 1, 3, 70, 78, 79, 81-84 be withdrawn.

Claims 1 and 21 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 17, and 33 of co-pending U.S. Application No. 11/592,097.

The Office has alleged that the claims of the instant application and the cited claims of the co-pending application are not patentably distinct because both teach a method of treating an autonomic nervous system abnormality such as a renal associated condition comprising administering an agent such as metoprolol, a beta blocker (Final Office Action of 4/12/2010, p. 7 and p. 38).

However, the Applicants contend that the current claims are directed to treatment of a condition caused by an autonomic nervous system abnormality using at least one beta-blocker. This is in contrast to the cited claims in the co-pending application, which are directed to a method of treating a renal associated condition comprising *selectively administering a pharmacological agent to the kidney by intrarenal infusion*, in a manner effective to treat said subject for said renal condition. The current claims also include administering at least one beta-blocker such that the parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system is *analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject.* This is in contrast to the cited claims in the co-pending application, which are directed to *increasing* the parasympathetic activity/sympathetic activity ratio such that *the parasympathetic function is at least substantially equal to the sympathetic function* in said portion of the autonomic nervous system.

Accordingly, the Applicants contend that the cited claims of co-pending U.S. Application No. 11/592,097 fails to teach or suggest every element of the rejected claims, and therefore, the requirements for a nonstatutory obviousness-type double-patenting rejection have not been met. The Applicants respectfully request

that the nonstatutory obviousness-type double-patenting rejection of Claims 1 and 21 be withdrawn.

Claim Rejection - 35 U.S.C. § 112

Claims 1, 3, 4, 11-28, 41, 62-84 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

In making the rejection, the Office continues to allege that the specification does not provide adequate support for the claimed invention because specific examples are not provided. The claimed invention is directed to the discovery by the inventors that *autonomic nervous system disturbances* are the *underlying cause of a wide range of diseases* that appear to be a heterogeneous, unrelated group of conditions. The inventors of the subject invention have therefore formulated pharmacologic strategies to treat various different disease conditions by *modulating autonomic function as the basis of therapy.*

The Applicants contend that ample evidence exists in the literature to support the inventors' discovery that autonomic nervous system disturbances are the underlying cause of a wide range of diseases that appear to be unrelated. For example, Lampert et al. have demonstrated that decreased parasympathetic tone is seen after acute myocardial infarction (abstract); Gambardella et al. have demonstrated that ANS dysfunction occurs and is responsible for the elevated BMR in elderly cancer patients (abstract); Ideker et al. demonstrate that monitoring parasympathetic and sympathetic nerve activity and stimulating the nerves as needed can prevent arrhythmia (abstract); Morita et al. disclose that the pathogenesis of Congenital Long QT Syndrome (LQTS) is thought to be closely related to autonomic nervous system abnormalities, and that use of an index of autonomic nervous activity can be useful for evaluating the severity of LQTS (abstract); Rang et al. discloses that associations between alterations in autonomic

control of the cardiovascular system and the development of hypertension in pregnancy has been a subject for investigation (abstract); and Guilli discloses evidence of impaired parasympathetic activity in some patients with cardiac Syndrome X (abstract).

The inventors have discovered that these diseases can be successfully treated with beta blockers (e.g., propranolol), by administering the beta blockers in manner and dose effective to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of a subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject. The drugs in question (e.g., beta blockers, and non-steroidal anti-inflammatory drugs (NSAIDs) are well-known agents, with well-known side-effects, which are used in well-known dosages.

The Applicants contend that in view of the support in the literature for the discovery that autonomic nervous system disturbances underlie many different diseases, and because the pharmacologic agents used in the subject methods are well-known to affect the autonomic nervous system, there is no evidence that use of the claimed pharmacological agents to treat the claimed diseases would not be successful. One of skill in the art would not need specific examples and doses in order to provide an adequate written description of this approach of modulating autonomic function to treat multiple diseases, as the Office suggests.

For example, the drugs in question (e.g., beta blockers, and non-steroidal anti-inflammatory drugs (NSAIDs) are well-known agents, with well-known side-effects, which are used in well-known dosages. In particular, the elected species propranolol is a well-known drug, which is being used in a standard dosage. The Applicants maintain that one of skill in the art would recognize that the specification when viewed in the context of the knowledge of those of ordinary skill in the art

provides sufficient written description support for the claims. The Applicants maintain that there is adequate support in the specification for the rejected claims directed to treatment methods for treating a condition caused by an autonomic nervous system abnormality, by using well-known drugs that are known to affect the autonomic nervous system. As such, the written description is sufficient to conclude that the inventors had possession of the claimed invention.

The Office continues to allege that the specification does not provide data or show any examples of actual administration of beta blockers along with a non-beta blocking agent in conditions arising from autonomic nervous system abnormality; that the specification does not teach administration of a non-beta blocker along with a beta blocker; and that the specification does not give any specific guidance to age associated conditions resulting from abnormality of autonomic nervous system regarding criteria for the dosages, the counter indications, dosage regimens, criteria if patients suffer from multiple associated conditions (Final Office Action of 4/12/2010, p. 8-9).

As discussed in the previous response, the specification does provide adequate description for methods of administering beta-blockers to treat a subject, for example, on p. 14, line 14 to p. 25, line 4. Disclosure of conditions that may be treated using the subject methods can be found, for example, on p. 56, lines 3-11, and p. 57, lines 10 to p. 59, line 11. Extensive support for the theory of pharmacologic strategies to treat various disease conditions by modulating autonomic function as the basis of therapy including multiple specific examples of diseases that can be treated along with references can be found on p. 4, line 9 to p. 5, line 26, and p. 59, line 11 to p. 67, line 29. There are specific examples disclosed in the specification, for example, as in the treatment of sudden infant death syndrome (SIDS), or conditions associated with aging. In the example of SIDS, (as disclosed on p. 59, lines 19-25, and p. 60, line 20 to p. 61, line 12) the inventors have discovered that a maladaptive shift to sympathetic bias may be a key determinant of SIDS, and cite multiple references in support of this assertion.

In the example of aging-associated conditions (as disclosed on p. 65, line 20 to p. 67, line 12), the inventors have determined that many conditions of aging are manifestations of sympathetic bias unmasked by withdrawal of parasympathetic function. Additional citations in support of this assertion can be found on p. 66, lines 13-27.

In summary, the inventors of the subject invention have discovered that autonomic nervous system disturbances are the underlying cause of a wide range of diseases, a relationship which is well-supported by evidence in the literature. The inventors have further discovered that these different diseases, which are thought to be unrelated, can be successfully treated with beta blockers (e.g., propranolol), by administering the beta blockers in manner and dose effective to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of a subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject. The Applicants contend that beta-blockers and NSAIDS are well-known drugs, and that optimization of dosages and management of side effects are routinely dealt with by physicians

Therefore, the Applicants maintain that there is adequate written description in the specification in sufficient detail that one skilled in the art can reasonably conclude that the inventors had possession of the claimed invention. The Examiner has not established with sufficient evidence why a person skilled in the art would not recognize that the written description of the invention provides support for the claims, and therefore, the Applicants respectfully request that the rejection of Claims 1, 3, 4, 11-28, 41, 62-84 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Claims 1, 3, 4, 11-28, 41, 62-84 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly being non-enabled by the specification.

In making the rejection, the Office again alleges that the specification does not provide sufficient guidance for the current claims. The Office alleges that the specification does not reasonably provide enablement for treating all the disorders listed in Claim 1, with the non-beta blocking agents listed in Claim 24 (Final Office Action of 4/12/2010, p 11).

The law regarding enablement of inventions is clear: "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation."[1]

Under *In re Wands*, a determination of enablement requires consideration of eight factors, including: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims.[2] Accordingly, under *In re Wands*, a determination of enablement is based on the combination of the factors, taken as a whole, not based solely on a single factor.

The Applicants contend that inventors of the subject invention have discovered that autonomic nervous system disturbances are the underlying cause of a wide range of disease conditions that appear to be a complex, heterogeneous, unrelated group. The present invention involves methods of treating conditions *that are caused by an autonomic nervous system abnormality*. In other words, the

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1. *United States v. Telectronics, Inc.*, 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). See also *Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

2. *Ex Parte Forman.*, 230 USPQ 546, 547 (Bd.Pat.App & Interf. 1986); and, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

conditions all contain the common element of being caused by an autonomic nervous system abnormality, and therefore, are not as broad as the Examiner suggests.

The claims are directed to a method of treating a subject for a condition caused by an autonomic nervous system abnormality, with a well-known agent (e.g., a beta-blocker), which for some of the conditions is a non-traditional agent, because the inventors have discovered that modulation of the autonomic nervous system can result in effective treatment for the condition. There is not, as the Examiner alleges, a requirement for testing each beta-blocker for all conditions listed, with every single non-beta blocker listed.

The inventors of the subject invention have therefore formulated pharmacologic strategies to treat conditions including disease conditions by modulating autonomic function as the basis of therapy. Extensive support for this theory including multiple specific examples of diseases that can be treated along with references can be found in the specification, for example on p. 4, line 9 to p. 5, line 26, and p. 59, line 11 to p. 67, line 29. Evidence from the literature to support the inventors' discovery that autonomic nervous system disturbances are the underlying cause of a wide range of diseases have been discussed above. Disclosure of conditions that may be treated using the subject methods can be found on p. 56, lines 3-11, and p. 57, line 10 to p. 59, line 11. There are specific examples disclosed in the specification, for example, as in the example of treatment of sudden infant death syndrome (SIDS), as disclosed on p. 59, lines 19-25, and p. 60, line 20 to p. 61, line 12. In this disclosure, the inventors have disclosed that a maladaptive shift to sympathetic bias may be a key determinant of SIDS, and additionally cited multiple references in support of this assertion. In the example of aging-associated conditions (as disclosed on p. 65, line 20 to p. 67, line 12), the inventors have determined that many conditions of aging are manifestations of sympathetic bias unmasked by withdrawal of parasympathetic

function. Additional citations in support of the assertion can be found on p. 66, lines 13-27.

Treatment is with agents that are well-known in the art, i.e., beta-blockers. Directions for treatment of the identified conditions by administering beta-blockers can be found, for example, on p. 14, line 14 to p. 25, line 4. Furthermore, the specification discloses methods of treating a condition such that the activities of the parasympathetic and sympathetic systems are modulated, for example, on p. 10, lines 11-27. Additionally, the specification discloses methods of determining the parasympathetic and sympathetic functions, for example, on p. 48, lines 24-29.

The arguments previously presented by the Applicants re: *In Re Wands*, as well as a discussion of the references provided by the Office still apply with the same force, however they will not be repeated in their entirety here. For the reasons set forth above as well as in the previous responses, the Applicants maintain that the enablement requirement to practice the method of treatment has been met because 1) the amount of experimentation required to practice the claimed methods would not be undue and excessive 2) guidance is given on how to practice such methods of treatment 3) it is not necessary to provide a working example, 4) the relative skill of those in the art is high, and 5) the breadth of claims is enabled by the specification. As such, one skilled in the art would be able to perform the experiments as a matter of routine. The specification, therefore, provides sufficient enablement such that one of ordinary skill in the art would be able to practice the invention without undue experimentation.

Accordingly, the Applicants maintain that the current claims directed to methods of treating a subject for a condition caused by an autonomic nervous system abnormality comprising providing a subject known to suffer from an autonomic nervous system abnormality, and administering to the subject an effective amount of at least one beta-blocker to produce a parasympathetic

activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject to treat the subject are sufficiently enabled by the specification.

In view of the foregoing discussion, the Applicants submit that the current claims are adequately enabled by the specification. Accordingly, the Applicants respectfully request that the rejection of Claims 1, 3, 4, 11-28, 41, 62-84 under 35 U.S.C. § 112, first paragraph be withdrawn.

Claim Rejections - 35 U.S.C. § 102

Claims 1, 3, 4, 14, 16, 19-22, 28, 41, 62, 76-79 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Gambardella et al. (Metabolism, 46, 3, March 1999, p. 291-297).

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, (Fed. Cir. 1987).

The standard for anticipation under section 102 is one of strict identity. An anticipation rejection requires a showing that each limitation of a claim be found in a single reference, *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984). Further, an anticipatory reference must be enabling, see *Akzo N.V. v. United States Int'l Trade Comm'n* 808 F.2d 1471, 1479, 1 U.S.P.Q.2d 1241, 1245 (Fed. Cir. 1986), cert denied, 482 U.S. 909 (1987), so as to place one of ordinary skill in possession of the claimed invention. To anticipate a claim, a prior art reference must disclose every feature of the claimed invention, either explicitly or inherently. *Glaxo v. Novopharm, Ltd.* 334 U.S. P.Q.2d 1565 (Fed. Cir. 1995).

An element of the rejected claims is a method of providing a subject known to suffer from an autonomic nervous system abnormality, and treating the subject by administering an effective amount of at least one beta-blocker to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject to treat a subject for the autonomic nervous system abnormality.

In rejecting the present claims, the Office has alleged that Gambardella teaches "administration of a beta blocker such as propranolol in patients suffering from cancer to treat an autonomic nervous system abnormality (e.g. cancer, see Applicants' Claim 41, cancer as one of the aging associated conditions caused by autonomic nervous system abnormality) (Final Office Action, p. 39; Office Action of 10/7/2009, p. 23). The Office asserts that because Gambardella allegedly meets the structural limitations of the claim, Gambardella therefore *inherently* teaches producing a parasympathetic activity/sympathetic activity ratio in at least a portion of the autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject.

However, the Applicants respectfully disagree. Gambardella discloses the use of propranolol in elderly weight-losing cancer patients to treat the weight loss by blocking the effects of the sympathetic nervous system. The goal of treatment disclosed in Gambardella is enhancement of daily caloric intake without increased energy expenditure (abstract).

In order to anticipate, the prior art reference "must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it." *In re Spada*, 911 F.2d 705, 708, 15 U.S.P.Q.2d (BNA) 1655, 1657 (Fed. Cir. 1990). Establishing inherency requires that the extrinsic evidence "must make clear that the missing descriptive matter is

necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. . . ."

The Applicants contend that the treatment in Gambardella is directed to reversing weight loss, and not treatment of cancer, as the Office asserts. Furthermore, Gambardella fails to teach the element of producing a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system *that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject.* Gambardella is silent with respect to this element, because the goal in Gambardella is treatment of weight loss, and there is no evidence that the method as in Gambardella would result in a ratio as in the current claims.

Accordingly, the Applicants maintain that Gambardella fails to anticipate the current claims, because Gambardella fails to teach each and every element of the rejected claims. Namely, Gambardella does not specifically disclose treating a condition by administering an effective amount of at least one beta-blocker to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject. Consequently, the Applicants respectfully request that the 35 U.S.C. § 102(b) rejection of Claims 1, 3, 4, 14, 19-22, 28, 41, and 62 be withdrawn.

Claims 1, 3, 4, 11-12, 15, 17, 21, 28, 41, 62, and 72 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Brevetti et al. (Brief communications, Nov. 1981, p 938-941).

In making this rejection, the Office alleges that Brevetti teaches administration of a beta blocker such as propranolol in patients suffering from Shy Drager syndrome, which is an autonomic nervous system abnormality. The Office asserts that because Brevetti allegedly meets the structural limitations of the claim,

Brevetti *inherently* teaches producing a parasympathetic activity/sympathetic activity ratio in at least a portion of the autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject (Final Office Action, p. 21).

However, the Applicants respectfully disagree. Brevetti was cited for disclosing treatment of an imbalance between the alpha- and beta-adrenoreceptor activity of the sympathetic nervous system (p. 941), however nowhere does Brevetti specifically disclose the element of administering an effective amount of at least one beta-blocker to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system *that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject.* The goal in Brevetti is treatment of low blood pressure. The Office has not pointed to any evidence that the method in Brevetti would result in a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject.

Accordingly, Brevetti fails to anticipate the current claims, because Brevetti fails to teach each and every element of the rejected claims. Namely, Brevetti does not specifically disclose treating a condition by administering an effective amount of at least one beta-blocker to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject. Consequently, the Applicants respectfully request that the 35 U.S.C. § 102(b) rejection of Claims 1, 3, 4, 11-12, 15, 17, 21, 28, 41, 62, and 72 be withdrawn.

Claims 1, 21, 23-25, 28, 69, and 74-76 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Davies, et al. (The J of Intl Med Research, 1988, 16, 173-181).

In making this rejection, the Office alleges that Davies teaches administration of a beta blocker such as propranolol in patients suffering from hypertension, an age-associated condition, which is also an autonomic nervous system abnormality. The Office asserts that because Davies allegedly meets the structural limitations of the claim, Davies *inherently* teaches producing a parasympathetic activity/sympathetic activity ratio in at least a portion of the autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject (Final Office Action, p. 22).

However, the Applicants respectfully disagree. Davies discloses that ibuprofen does not substantially affect treatment of hypertension in patients on beta-blockers or thiazides, however there is no discussion in Davies of the autonomic nervous system. Nowhere does Davies specifically disclose the element of administering an effective amount of at least one beta-blocker to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system *that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject*, nor has the Office pointed to evidence that the method in Davies would result in a ratio as in the current claims.

Accordingly, Davies fails to anticipate the current claims, because Davies fails to teach each and every element of the rejected claims. Namely, Davies does not specifically disclose treating a condition by administering an effective amount of at least one beta-blocker to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a

healthy 25 year old human subject. Consequently, the Applicants respectfully request that the 35 U.S.C. § 102(b) rejection of Claims 1, 21, 23-25, 28, 69, and 74-76 be withdrawn.

Claims 1, 16, and 18 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Bugiardini, et al. (Am J Cardiol, 1989, Feb 1, 63, 5, 286-90) as evidenced by Guilli, et al. (Cardiovascular Research, 2001, 208-216).

In making the rejection, the Office alleges that Bugiardini teaches administration of propranolol to patients with X syndrome, which reduces the number of ischemic episodes per 24 hours (abstract). Guilli teach that patients with cardiac X syndrome exhibit reduced parasympathetic activity and normal sympathetic activity (abstract). The Office asserts that because Bugiardini as evidenced by Guilli allegedly meets the structural limitations of the claim, that Bugiardini *inherently* teaches producing a parasympathetic activity/sympathetic activity ratio in at least a portion of the autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject (Final Office Action, p. 23).

However, nowhere does Bugiardini specifically disclose the element of administering an effective amount of at least one beta-blocker to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system *that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject.* The Office has not pointed to where Bugiardini teaches the element of achieving a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject.

Accordingly, Bugiardini as evidenced by Guilli fails to anticipate the current claims, because Bugiardini fails to teach each and every element of the rejected

claims. Namely, Bugiardini does not disclose treating a condition by administering an effective amount of at least one beta-blocker to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject. Consequently, the Applicants respectfully request that the 35 U.S.C. § 102(b) rejection of Claims 1, 16, and 18 be withdrawn.

Claims 1 and 13 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Shimizu, et al. (J of the Amer. College of Cardiology, 39, 12, June 2002) as evidenced by Morita, et al. (Jpn Circ J 1996, Oct 60(10), 742-8).

In making the rejection, the Office alleges that Shimizu teaches administration of propranolol to patients with LQT syndrome under normal tone or during sympathetic stimulation, and that Morita teaches that LQTs patients have autonomic nervous system abnormalities. The Office asserts that because Shimizu as evidenced by Morita allegedly meets the structural limitations of the claim, that Shimizu *inherently* teaches producing a parasympathetic activity/sympathetic activity ratio in at least a portion of the autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject (Final Office Action, p. 24).

However, nowhere does Shimizu specifically disclose the element of administering an effective amount of at least one beta-blocker to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system *that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject.* The Office has not pointed to where the method in Shimizu would *necessarily* achieve a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject.

Accordingly, Shimizu as evidenced by Morita fails to anticipate the current claims, because Shimizu fails to teach each and every element of the rejected claims. Namely, Shimizu does not disclose treating a condition by administering an effective amount of at least one beta-blocker to produce a parasympathetic activity/sympathetic activity ratio in at least a portion of said subject's autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject. Consequently, the Applicants respectfully request that the 35 U.S.C. § 102(b) rejection of Claims 1 and 13 be withdrawn.

Claim Rejections - 35 U.S.C. § 103

Claims 1, 63, 70, 71 and 73 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Lampert et al. (The Am J of Cardiology, 91, 2, Jan 2003) and Gambardella et al. (Metabolism, 46, 3, March 1999, p. 291-297) in view of Ideker et al. (U.S. Patent No. 5,522,854)

In order to meet its burden in establishing a rejection under 35 U.S.C. §103, the Office must first demonstrate that a prior art reference, or references when combined, teach or suggest all claim elements. See, e.g., *KSR Int'l Co. v. Teleflex* Inc., 127 S.Ct. 1727, 1740 (2007); *Pharmastem Therapeutics v. Viacell et al.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007); MPEP § 2143(A)(1). In addition to demonstrating that all elements were known in the prior art, the Office must also articulate a reason for combining the elements. See, e.g., KSR at 1741; *Omegaflex, Inc. v. Parker-Hannifin Corp.*, 243 Fed. Appx. 592, 595-596 (Fed. Cir. 2007) citing KSR. Further, the Supreme Court in KSR also stated that that "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions." KSR at 1740; emphasis added. As such, in addition to showing that all elements of a claim were known in the prior art and that one of ordinary skill in the art had a reason to combine them,

the Office must also provide evidence that the combination would be a predicted success.

In making the rejection, the Office alleges that Lampert teaches that propranolol therapy improves recovery of parasympathetic tone in patients with acute myocardial infarction. The Office asserts that although the reference does not explicitly teach that administration of beta blockers produces a parasympathetic activity/sympathetic activity ratio in at least a portion of the autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject, however that Lampert teaches administration of similar doses of propranolol as in the instant specification (Final Office Action, p. 25).

However, the Applicants maintain that Lampert does not teach the element of *providing* a subject known to suffer from an autonomic nervous system abnormality. Further, there is no disclosure in Lampert that teaches or suggests that the treatment will *necessarily* result in a parasympathetic activity/sympathetic activity ratio in at least a portion of the autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject.

Lampert further does not suggest these elements, because the study was designed to "elucidate the mechanisms by which ß blockers decrease mortality after acute myocardial infarction". There is therefore no suggestion of *providing* a subject known to suffer from an autonomic nervous system abnormality. There is also no suggestion of producing a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject.

Ideker was cited for allegedly teaching measuring heart rate variability, with a decrease in heart rate variability indicating an increased risk of arrhythmia. However as neither reference teaches *providing* a subject known to suffer from an autonomic nervous system abnormality, or of producing *a parasympathetic activity/sympathetic activity ratio in at least a portion of the autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject*, the combination of the references fails to teach or suggest all the elements of the current claims.

The Office further alleges that although Lampert does not teach determining a ratio of parasympathetic activity/sympathetic activity, Ideker, et al. allegedly teach that a preferred way of measuring the ratio of sympathetic to parasympathetic nerve activity is to measure heart rate variability, with a decrease in heart rate variability indicating an increased risk of arrhythmia (col. 3, lines 49-52). The Office alleges that one of ordinary skill in the art would have been motivated to determine the parasympathetic/sympathetic activity ratio in at least a portion of the ANS to use the ratio as an indicator of whether there is a decrease in heart rate variability that is associated with an increased risk of the onset of arrythmia (Office Action of 10/7/2009, p. 29-30).

However, the Office has not articulated a sufficient reason why one of skill in the art would look to a ratio for assessing risk of *arrhythmia* as in Ideker in using the method of Lampert. Lampert is directed to using propranolol to decrease the "combined outcome of death, myocardial infarction, or congestive heart failure" after acute myocardial infarction (AMI) (p. 140, col. 1, para. 1). Ideker is directed to a method for detecting a high risk of arrythmia and preventing arrhythmia by afferent nerve stimulation (abstract). To the extent that Ideker discloses determining the ratio of sympathetic nerve activity to parasympathetic nerve activity, it is for the purpose of detecting a high risk of *arrhythmia* (col. 1, lines 53 to 56). The Office has therefore not provided any reason why one of skill in the art would "use the ratio [of Ideker] as an indicator of whether there is a decrease in

heart rate variability that is associated with an increased risk of the onset of arrythmia" in the method of Lampert, because Lampert is directed to assessing the risk of *death, myocardial infarction, or congestive heart failure* after acute myocardial infarction, and not arrhythmia.

Furthermore, the Applicants contend that the reasoning relied upon by the Office must not come solely from the description of the Applicants' invention in their specification. If it does, the Examiner used impermissible hindsight when rejecting the claims. See *W.L. Gore & Associates v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984); *In re Rothermel*, 276 F.2d 393, 396 (CCPA 1960)." (See BPAI decision of 1/15/2009 *Ex parte* Vogel, Ognibene, Bench, and Peaslee; Appeal 2008-5921)

The Applicants contend that the Office has not shown sufficient reason why one of ordinary skill in the art would have been led by the disclosure in Lampert (use of propranolol to improve recovery of parasympathetic tone in patients after AMI by assessing the outcomes of death, myocardial infarction, or congestive heart failure) to use the ratio as disclosed in Ideker (using a ratio for the purpose of detecting a high risk of arrhythmia).

Therefore, the Applicants maintain that the Office does not have support in Lampert's disclosure for the combination with Ideker. In fact, the reasoning relied upon by the Office for combining the two references appears to derive solely from the description of the Applicant's invention in their specification. The Office appears to be proposing a modification of the assessment of the risk of sudden death after AMI in Lampert by using the sympathetic activity/parasympathetic activity ratio for detecting a high risk of arrhythmia disclosed in Ideker. The Examiner's rationale for modifying Lampert's method with the ratio of Ideker therefore appears to be based upon impermissible hindsight.

Therefore, a prima facie case of obviousness has not been established because none of the cited references teach or suggest the elements of *providing* a subject known to suffer from an autonomic nervous system abnormality, or of administering a beta-blocker to produce *a parasympathetic activity/sympathetic activity ratio analogous to the ratio observed in a healthy 25 year old human subject* in at least a portion of the autonomic nervous system. The combination therefore does not contain all the elements of the claimed invention, and does not render the claimed invention obvious. Furthermore, none of the references teach or suggest administering an effective amount of at least one beta blocker in response to a *determined sympathetic activity/parasympathetic activity ratio*, as in Claim 71. In addition, the Office has not articulated a sufficient reason why one skilled in the art would have modified the method in Lampert with the ratio in Ideker. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 1, 63, 70 and 71 be withdrawn.

Claims 64-68 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Gambardella et al. (Metabolism, 46, 3, March 1999, p. 291-297) as applied to Claims 1, 3, 4, 14, 16, 19-22, 28, 41, and 62 above in view of Mann et al. (US 2004/0147969).

In making this rejection, the Office cites Gambardella for teaching the use of propranolol in elderly weight-losing cancer patients to block the effects of the sympathetic nervous system. However, Gambardella does not teach the elements of *providing* a subject known to suffer from an autonomic nervous system abnormality, or of administering a beta-blocker in an amount effective to produce *a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human*, because Gambardella is directed to enhancement of daily caloric intake without increased energy expenditure (abstract). There is further no suggestion of these

elements, because Gambardella is directed to enhancement of daily caloric intake without increased energy expenditure (abstract).

The Office acknowledges that Gambardella does not explicitly teach employing a control feedback loop, as in Claims 64-68. The Office therefore cites Mann for allegedly teaching therapeutic treatment for cardiac disease comprising sensors, and that patients can be titrated to appropriate beta-blocker dose levels based on the signals (Final Office Action, p. 27).

However as neither reference teaches *providing* a subject known to suffer from an autonomic nervous system abnormality, or of producing *a parasympathetic activity/sympathetic activity ratio in at least a portion of the autonomic nervous system that is analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human subject*, the combination of the references fails to teach or suggest all the elements of the current claims.

The Office alleges that it would have been obvious to have employed a control feedback loop in treating autonomic nervous dysfunctions from the teachings of Mann, because "one having ordinary skill in the art at the time of the invention would have been motivated in employing a control feed back loop in expectation of life saving therapeutic benefits by using parameter-driven adjustment therapy by using indicators such as sensors because based on output of signal from the sensor, the therapeutic treatment can be adjusted to help the patient's medical conditions" and further, "it would have been obvious to one having ordinary skill in the art at the time of the invention that modulation of autonomic nervous system can be monitored and detected using sensor in patients with such conditions and will be able to regulate the sympathetic and parasympathetic systems using beta blockers such as propranolol" (Final Office Action, p. 28).

However, the Office has not articulated a sufficient reason why one of skill in the art would look to a system for treating cardiovascular disease as in Mann in using the method of Gambardella. Gambardella is directed to using propranolol to enhance daily caloric intake in elderly cancer patients, without increasing energy expenditure (abstract). Mann is directed to an apparatus for treating cardiovascular disease, using left atrial blood pressure sensors (abstract, para. 380). To the extent that Mann discloses use of a control feedback loop, it is for the purpose of treating cardiovascular disease. The Office has therefore not provided any reason why one of skill in the art "would have been motivated in employing a control feed back loop in expectation of life saving therapeutic benefits by using parameter-driven adjustment therapy by using indicators such as sensors because based on output of signal from the sensor, the therapeutic treatment can be adjusted to help the patient's medical conditions"" in the method of Gambardella, because Gambardella is directed to enhancement of daily caloric intake without increased energy expenditure in elderly cancer patients, and not to treatment of cardiovascular disease.

Furthermore, the Applicants contend that the reasoning relied upon by the Office must not come solely from the description of the Applicants' invention in their specification. If it does, the Examiner used impermissible hindsight when rejecting the claims. See *W.L. Gore & Associates v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984); *In re Rothermel*, 276 F.2d 393, 396 (CCPA 1960)." (See BPAI decision of 1/15/2009 *Ex parte* Vogel, Ognibene, Bench, and Peaslee; Appeal 2008-5921)

For the reasons discussed above, the Applicants contend that the Office has not shown sufficient reason why one of ordinary skill in the art would have been led by the disclosure in Gambardella to use the ratio as disclosed in Mann.

Therefore, the Applicants maintain that the Office does not have support in Gambardella's disclosure for the combination with Mann. In fact, the reasoning

relied upon by the Office for combining the two references appears to derive solely from the description of the Applicant's invention in their specification. The Office appears to be proposing a modification of the treatment of weight losing elderly cancer patients in Gambardella by using the control feedback loop, using left atrial blood pressure sensors, for treating cardiovascular disease disclosed in Mann. The Examiner's rationale for modifying Gambardella's method with the ratio of Mann therefore appears to be based upon impermissible hindsight.

Therefore, a prima facie case of obviousness has not been established because none of the cited references teach or suggest the element of *providing* a subject known to suffer from an autonomic nervous system abnormality, or of administering a beta-blocker to produce *a parasympathetic activity/sympathetic activity ratio analogous to the ratio observed in a healthy 25 year old human subject* in at least a portion of the autonomic nervous system. The combination therefore does not contain all the elements of the claimed invention, and does not render the claimed invention obvious. In addition, the Office has not articulated a sufficient reason why one skilled in the art would have modified the method in Gambardella with the control feedback loop in Mann. Therefore, the combination of references does not render the current claims obvious. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 64-68 be withdrawn.

Claims 80-81 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Gambardella et al. (Metabolism, 46, 3, March 1999, p. 291-297) as applied to Claims 1, 3, 4, 14, 16, 19-22, 28, 41, 62, 76-79 above and in view of Walsh et al. (Support Care Cancer 2002, 10:523-528).

In making this rejection, the Office acknowledges that Gambardella does not explicitly teach determination of parasympathetic and sympathetic activity ratio in at least a portion of the subject's autonomic nervous system, as in Claims 80-81. The Office therefore cites Walsh for allegedly teaching methods of measuring

parasympathetic and sympathetic functions of the ANS in cancer patients. The Office alleges it would have been obvious to one of ordinary skill in the art to use the method of Nelson to measure the parasympathetic and sympathetic activities to evaluate symptoms associated with ANS abnormalities (Final Office Action, p. 29).

However, the Examiner has failed to show where Walsh teaches determination of the parasympathetic and sympathetic activity *ratio*, or where Walsh teaches *administering an effective amount of at least one beta-blocker to said subject in response to said determined parasympathetic activity/sympathetic activity ratio,* as in the rejected claims.

Further, neither reference teaches the element of administering a beta-blocker in an amount effective to produce *a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human.* Neither reference suggests this element, because Gambardella is directed to enhancement of daily caloric intake without increased energy expenditure (abstract), and Walsh is directed to documenting ANS dysfunction in advanced cancer, with no suggestion of treatment (see abstract).

Therefore, a *prima facie* case of obviousness has not been established because the cited references fail to teach or suggest the elements of determination of the parasympathetic and sympathetic activity *ratio*, or of *administering an effective amount of at least one beta-blocker to said subject in response to said determined parasympathetic activity/sympathetic activity ratio.* Further, neither reference teaches or suggests administering a beta-blocker to produce *a parasympathetic activity/sympathetic activity ratio analogous to the ratio observed in a healthy 25 year old human subject* in at least a portion of the autonomic nervous system. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 80-81 be withdrawn.

Claims 82-84 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Gambardella et al. (Metabolism, 46, 3, March 1999, p. 291-297) as applied to Claims 1, 3, 4, 14, 16, 19-22, 28, 41, 62, 76-79 above and in view of Jatoi et al. (*Current Management of Cancer-Associated Anorexia and Weight Loss,* Oncology, 2001).

In making this rejection, the Office acknowledges that Gambardella does not explicitly teach administration of an NSAID. The Office therefore cites Jatoi for allegedly teaching that NSAIDs such as ibuprofen can be used to halt the wasting process associated with cancer associated weight loss. The Office alleges it would have been obvious to one of ordinary skill in the art to have administered an NSAID in treating weight loss associated with cancer (Final Office Action, p. 30).

However, as discussed above, Gambardella fails to teach administering a beta-blocker in an amount effective to produce *a parasympathetic activity/sympathetic activity ratio in at least a portion of the subject's autonomic nervous system analogous to the parasympathetic activity/sympathetic activity ratio observed in a healthy 25 year old human*, because Gambardella is directed to enhancement of daily caloric intake without increased energy expenditure (abstract). There is further no suggestion of this element, because Gambardella is directed to enhancement of daily caloric intake without increased energy expenditure (abstract).

Jatoi was cited by the Office for teaching that NSAIDs such as ibuprofen can be used to halt the wasting process seen with cancer associated weight loss, however as Gambardella fails to teach all the element of the claimed invention, Jatoi fails to make up for this deficiency.

Therefore, a *prima facie* case of obviousness has not been established because the cited references fail to teach or suggest administering a beta-blocker

to produce *a parasympathetic activity/sympathetic activity ratio analogous to the ratio observed in a healthy 25 year old human subject* in at least a portion of the autonomic nervous system. Consequently, the Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of Claims 82-84 be withdrawn.

CONCLUSION

The Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number PALO-002.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

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Enc:
- Terminal Disclaimer over co-pending U.S. Application No. 11/060,643 (PALO-001 CIP2)
- Terminal Disclaimer over co-pending U.S. Application No. 10/962,190 (PALO-005)

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